HFA-305

Date of Approval: JUN 3 2004

FREEDOM OF INFORMATION SUMMARY

NADA 141-229

SEDIVET 1% Injection

romifidine hydrochloride

SEDIVET 1% Injection is indicated for use as a sedative and analgesic to facilitate handling, clinical examinations, clinical procedures, and minor surgical procedures in adult horses. SEDIVET 1% Injection is also indicated as a preanesthetic prior to the induction of general anesthesia in adult horses.

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

141-229

FOIS 1

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1. GENERAL INFORMATION:

a. File Number:	NADA 141-229
b. Sponsor:	Boehringer Ingelheim Vetmedica, Inc. 2621 North Belt Highway St. Joseph, MO 64506-2002 Drug Labeler Code: 000010
c. Established Name:	romifidine hydrochloride
d. Proprietary Name:	SEDIVET 1% Injection
e. Dosage Form:	sterile injectable solution
f. How Supplied:	20 mL glass vial
g. How Dispensed:	R_x
h. Amount of Active Ingredients:	10 mg/mL
i. Route of Administration:	single intravenous injection
j. Species/Class:	horses
k. Recommended Dosage:	*Sedation and Analgesia:* 40 - 120 mcg/kg (0.4 - 1.2 mL/100 kg body weight) *Preanesthesia:* 100 mcg/kg (1.0 mL/100 kg body weight)
l. Pharmacological Category:	alpha$_2$-adrenergic agonist
m. Indications:	SEDIVET 1% Injection is indicated for use as a sedative and analgesic to facilitate handling, clinical examinations, clinical procedures, and minor surgical procedures in adult horses. SEDIVET 1% Injection is also indicated as a preanesthetic prior to the induction of general anesthesia in adult horses.

2. EFFECTIVENESS:

a. Dosage Characterization:

(1) Study on the Effect of Romifidine in Horses: Sedation and Analgesia for Procedures in the Region of the Head and Neck (SVC 105):

This field study conducted in Germany examined the sedative and analgesic effects of romifidine for procedures in the region of the head and neck (for example, endoscopy; radiography). Horses (n = 117) received IV doses of 40 or 80 mcg/kg. Investigators were masked to the romifidine dose. Dose dependent effects were noted for quality of sedation (deeper with the higher dose), quality of analgesia (increased tolerance), head ptosis (more marked), and sedation-related movements (more swaying and ataxia). Analgesia was not evaluated separately.

There were no clinically relevant differences between dose groups for the onset or duration of either sedation (table shows mean values for time).

Dose	Onset sedation	Duration sedation
40 mcg/kg IV	2 minutes	55 minutes
80 mcg/kg IV	2 minutes	62 minutes

(2) Study on the Effect of Romifidine in Horses: Sedation for Manipulations in the Regions of the Thorax, Abdomen, and Limbs (SVC 107):

Another German field study (n = 128) investigated the sedative and analgesic effects of romifidine for procedures in the region of the thorax, abdomen, and limbs. Procedures included rectal and vaginal examinations, radiography, clipping, wound cleansing, etc. Analgesia was not evaluated separately. Investigators were masked to the romifidine dose. At IV doses of 80 and 120 mcg/kg, no clinically relevant dose related differences were noted for onset and duration (table shows mean values for time).

Dose	Onset sedation	Duration sedation
80 mcg/kg IV	3 minutes	91 minutes
120 mcg/kg IV	2 minutes	84 minutes

The quality of sedation differed only in that there were fewer defensive reactions in the higher dose group for manipulations involving the forelimbs. For both dose groups, more defensive movements were noted during manipulations of the hindlimbs. Three (of forty-nine) hind limb procedures could not be performed (two in the lower dose group and one in the higher dose group), due to defensive movements.

Mild abdominal pain was reported four times as an adverse reaction. Other side effects, such as sweating, ataxia, and atrioventricular heart block, are comparable with other alpha$_2$-agonists in horses.

Conclusion on dosage characterization:

The results of these two European studies provide data supporting a dose range between 40-120 mcg/kg for IV romifidine. This dose range was used for field studies in Canada and the United States.

b. Substantial Evidence:

Canadian Field Study:

Title: An investigation of the safety and effectiveness of romifidine when used for sedation and preanesthesia in the horse.

(1) Type of study: field study

(2) Investigators:

Dr. W. McDonell, DVM, PhD, DVA, Diplomate ACVA
Guelph, Ontario, Canada
Dr. S. Young, Vet.MB, PhD, MRCVS, DVA
Guelph, Ontario, Canada
Dr. C. Kerr, DVM
Guelph, Ontario, Canada

(3) General Design:

(a) *Purpose:* To evaluate the effectiveness of SEDIVET for sedation/analgesia or preanesthesia in the horse.

(b) *Test Animals:* 23 adult horses in sedation trial
22 adult horses; one foal in preanesthesia trial

(c) *Control Drug:* N/A; investigators were not masked

(d) *Dosage Form:* sterile injectable solution (market formulation)

(e) *Route of Administration:* a single, slow, intravenous injection (jugular)

(f) *Dosage Used:* Sedative doses ranged between 30 and 100 mcg/kg; preanesthetic doses ranged between 40 and 100 mcg/kg.

Clinicians selected the dose that they felt was appropriate for each procedure.

(g) *Test Duration:* single administration

(h) *Variables Measured:*

Sedation study variables:

The following objective observations were evaluated:

time to onset of sedation
duration of sedation
sedation adequate or inadequate to accomplish procedure
additional physical or chemical restraint required
heart rate (HR)
respiratory rate (RR)
side effects related to romifidine (sweating, piloerection, urination, respiratory stridor, etc.)
adverse reactions

The following subjective variables were evaluated:

pre-sedation temperament
degree of ataxia
quality of sedation for the intended procedure

Preanesthesia study variables:

The following variables were evaluated:

assessment of temperament and health status
assessment of anesthesia
ease of movement after sedation
induction and recovery from anesthesia
adverse events during anesthesia or perioperatively

(4) Statistical Analysis: Descriptive statistics were used.

(5) Results:

(a) *Sedation study:*

Four horses were dosed at 30 mcg/kg, sixteen horses received 40 mcg/kg, two received 60 mcg/kg and one received 100 mcg/kg. Procedures were satisfactorily completed, and included endoscopy, bronchoalveolar lavage, radiography, gastroscopy, and cerebrospinal fluid collection. The duration of sedation lasted from 30 to 60 minutes in eighteen cases. One horse remained sedated for 90 minutes. The remaining four horses were observed for the duration of the procedure and the duration of sedation was not recorded.

Of the twenty-three horses, poor sedation was reported for two horses, fair in three horses, and good or excellent in eighteen horses. Additional restraint (twitch) was applied in eighteen of twenty-three cases.

Side effects were minimal and related to the class of alpha-$_2$-agonist drugs (ataxia, bradycardia, lowered head carriage).

(b) *Preanesthesia study:*

Twenty horses were induced with ketamine, two with barbiturates, and one foal was anesthetized with isoflurane through a nasotracheal tube.

Ten demonstration horses were anesthetized without surgery. Four horses were castrated, three had eye surgery, four required orthopedic procedures, one wound was debrided, and one horse was anesthetized for radiography.

At the investigator's discretion, romifidine preanesthetic doses ranged between 40 and 100 mcg/kg IV. Most horses that received ketamine as the anesthetic induction agent received higher romifidine doses (80-100 mcg/kg). Some ketamine inductions also included diazepam as a preanesthetic. When guaifenesin was included as a preanesthetic muscle relaxant prior to ketamine or barbiturate induction, lower romifidine doses were used.

The onset of sedation ranged from 30 to 120 seconds following romifidine administration (mean 67.2 seconds). Fifteen horses were easily moved after sedation; four were reluctant to move (four assessments were not recorded). Assessment of the quality of induction showed sixteen of the horses having well-controlled inductions (seven assessments were not recorded). Recovery from anesthesia was evaluated as "satisfactory" or "excellent" in twenty-one (of 23) horses; none experienced stormy recoveries.

(6) Conclusions:

(a) *Sedation study:* Satisfactory clinical sedation and safety were demonstrated. However, to avoid ineffectiveness and the necessity for additional restraint, higher doses of romifidine may be administered.

(b) *Preanesthesia study:*

The preanesthesia study demonstrated the effectiveness and compatibility of romifidine with commonly used drugs associated with anesthesia in twenty-two horses. Horses demonstrated acceptable anesthetic induction and recovery when romifidine was used as a preanesthetic. Side effects, compatibility, sedative and analgesic effects are similar, compared to other alpha$_2$-agonists. Romifidine was evaluated in only one foal that subsequently experienced an adverse reaction (see Adverse Reactions below). Inadequate data exist regarding the use of romifidine in foals; therefore, romifidine is recommended for use in adult horses only.

(7) Adverse Reactions:

(a) *Sedation study:* Side effects were minimal and related to the class of alpha-$_2$-agonist drugs (ataxia, bradycardia, lowered head carriage). Ineffectiveness was related to doses at the lower end of the recommended dose range.

(b) *Preanesthesia study:*

Bradycardia (HR < 30 beats per minute) was an expected side effect, that is seen with other alpha-$_2$-agonists. Four horses that received higher romifidine doses and ketamine induction (without diazepam or guaifenesin preanesthesia) required the use of the lip twitch for additional restraint.

A five week old foal received 40 mcg/kg romifidine prior to induction, and appeared adequately sedated. The foal was induced and maintained using isoflurane. Isoflurane vaporizer levels were initially high (3.0 to 3.5%) to accomplish induction. The foal became bradycardic and hypotensive during ventilated anesthesia. Dobutamine and fluids were administered and the foal's cardiovascular state was stabilized.

Sedation Dose Confirmation Study:

Title: Dose Confirmation of SEDIVET 1% Injection (Romifidine HCl), an α_2-Agonist with Sedative and Analgesic Properties for Use in the Horse (635-0290-97E-005)

(1) Type of Study: Dose confirmation clinical study

(2) Investigators: J. Smith
Baton Rouge, LA

(3) General Design:

(a) *Purpose:* To confirm the effectiveness of the proposed dose range of SEDIVET for sedation and analgesia in the horse.

(b) *Test Animals:* *Number* —20 horses used in a crossover design
Sex —10 mares and 10 geldings
Breed —18 Thoroughbreds and 2 Quarter Horses
Age —3 to 18 years of age
Weight —969 to 1235 lb (440 to 561 kg)

(c) *Control Drug:* N/A

(d) *Dosage Form:* sterile injectable solution (market formulation)

(e) *Route of Administration:* a single, slow, intravenous injection (jugular)

(f) *Dosage Used:* 40 mcg/kg (0.4 mL/100 kg, or 0.18 mL/100 lb) body weight
120 mcg/kg (1.2 mL/100 kg, or 0.54 mL/100 lb) body weight

(g) *Test Duration:* single administration

(h) *Variables Measured:*

Clinical Evaluations:

1. Stance / posture	8. Respiratory
2. Behavioral attitude	9. Penis relaxation (geldings)
3. Eyelid drooping	10. Sweating
4. Lower lip drooping / lip separation	11. Skin temperature
5. Facial edema	12. Clinical assessment of depth of sedation
6. Salivation	13. Clinical assessment of degree of analgesia
7. Cardiovascular	14. Other observations/comments

Objective Variables:

1. Head ptosis	5. Rectal temperature
2. Ear ptosis	6. Hoof withdrawal reflex latency (HWRL)
3. Respiratory rate	7. Skin twitch reflex latency (STRL)
4. Cardiac rate, rhythm (ausculted)	

Other evaluations: Physical examination, hematology and serum chemistry (prior to first treatment and 7 days after final treatment)

(4) Statistical Analyses:

The variables fell into two categories: continuous, and categorical (dichotomous, ordinal, and nominal) variables.

Continuous variables. Continuous clinical evaluation responses were analyzed using a repeated measures methodology based on a crossover design to test for differences between treatment groups.

Categorical variables. Categorical variables were analyzed at each observation period to test for agreement or disagreement of responses for the two treatment groups using analysis that recognized the crossover design including the assumption that there is no effect due to the different treatment periods nor do carryover effects from the first treatment exist.

The ordinal variables were analyzed at each observation point to test for agreement and trends of responses for the two treatment groups. Two assumptions for this test are: there is no effect due to the different treatment periods nor do carryover effects from the first treatment received exist.

The nominal variables were analyzed at each observation period to test for agreement of the response between each of the two treatment groups. Identical assumptions exist for nominal variables as did for categorical variables.

(5) Results:

This study employed two treatment groups. Twenty horses received each of two dosages (40 and 120 mcg romifidine/kg body weight) intravenously in a double-masked, crossover design. There was a minimum seven-day washout between treatments. Sedation-related variables, nociceptive threshold variables, and safety variables were observed at -30, -20, and -10 minutes prior to injection, and at 5, 15, 30, 45, 60, 75, 90, 105, 120, 150, and 180 minutes post injection.

Clinical Assessment of Depth and Duration of Sedation: Clinical assessment of sedation, in which both depth and duration of sedation were subjectively assessed, was dose dependent. The mean score indicated deeper sedation at each time point for the higher compared to the lower dose ($p<0.05$). Sedation returned to baseline by 150-180 minutes for the low dose, but was still different from the baseline at 180 minutes for the high dose ($p<0.05$).

Behavioral Attitude: The clinical assessment of sedation was supported by a dose-related response for the subjective evaluation of behavioral attitude. Behaviorally, all horses were sedated through 45 minutes for the lower dose; all horses (except one at 15 minutes) were sedated through 60 minutes for the higher dose. After these times, in a dose-related fashion, horses gradually became alert over the remainder of the study period.

General Sedation Variables: Other responses indicative of sedation (head ptosis, ear ptosis, stance/posture, lip drooping, and eyelid drooping) were also dose-related.

Facial edema and salivation were increased in the high dose group. Penis relaxation occurred in all male horses, but relaxation occurred in most horses later with the high dose (at 90 minutes) compared to the low dose (within five minutes).

General Analgesia: Analgesic responses were evaluated by the time to hoof withdrawal, by clinical assessments of hoof withdrawal (HWRL), and skin twitch (STRL) reflexes. In the presence of a treatment-by-sex-by-baseline interaction, STRL was greater ($p<0.05$) for the higher dose for both genders. This observation was supported by the clinical assessment of STRL. Similarly, HWRL was greater ($p<0.05$) for the higher dose over most of the observation period through 120 minutes, and the clinical assessment of the HWRL was greater ($p<0.05$) for the high dose through 150 minutes. Clinically, analgesia was judged to be better and more prolonged in response to a thermal stimulus on the fetlock compared to the response to a thermal stimulus over the withers.

Heart Rate and Rhythm: Heart rate was decreased throughout the post-treatment observation period for both dosages ($p<0.05$), and the decrease was dose-dependent through at least 120 minutes ($p<0.05$). The frequency of arrhythmias, characterized as second degree atrioventricular (AV) block, was at times sequential, and was increased following treatment with romifidine. This increase was dose-dependent. The incidence of arrhythmias declined as heart rate increased and signs of sedation were no longer observed.

Pulse Characteristic: Pulse was characterized as weak, sweating increased, and oral mucous membrane color appeared to be affected in a dose and time dependent manner. Significantly, more horses on the high dose had "purple" membranes from 30 to 105 minutes post-injection ($p<0.05$). Though this clinical observation can sometimes be used to evaluate heart function, in this study, purple oral mucous membranes were more likely related to the horses having their heads lowered, resulting in venous congestion.

Respiratory Rate: Both doses significantly ($p<0.05$) lowered the respiratory rate compared to the baseline mean throughout the post-treatment period with a similar pattern in each dose group. These data suggest that the lowering of the respiratory rate is not dose dependent. The overall effect on ventilation could not be assessed because tidal volume and blood gases were not measured.

Respiratory Characteristics: Respiratory character was altered post-treatment, but there was no statistically significant difference between the two doses ($p>0.05$). Deep or deep/slow breaths were the most commonly reported alterations. No respiratory distress was seen in any of the horses.

Respiratory Sounds: The higher dose appeared to increase the frequency of upper respiratory sounds, but this was statistically significant only at 45 minutes ($p<0.05$).

This increase in upper respiratory sounds was likely a secondary effect due to the lowered head, resulting in partial obstruction of the nasal passages due to tissue edema. None of the horses required that their heads be elevated to maintain open nasal passages.

Nasal Discharge: Following romifidine administration, horses in 16 out of the 40 total doses exhibited slight to moderate nasal discharge at more than two time points. The number of horses with a slight serous nasal discharge in the high dose group increased over time; this was not observed with the low dose. Nasal discharge was also a likely secondary effect as a result of head ptosis.

Rectal Temperature: Both doses produced a transient increase in rectal temperature from baseline (increased for 30 minutes in low dose and for 60 minutes in high dose) followed by a statistically lower mean temperature from 60-180 minutes for the lower dose ($p<0.05$), and from 90-180 minutes for the higher dose ($p<0.05$). The mean rectal temperature remained within one degree of the mean baseline temperature; however, a low temperature of 97.1 °F was observed in both dose groups.

Miscellaneous Physiological Responses: A variety of other physiological responses were evaluated. There was no change from baseline for heart sounds, capillary refill time, mucous membrane hydration, and lower respiratory sounds. Blood analyses and physical examinations, performed seven days following the final treatment administration revealed no clinically significant changes.

(6) Conclusions:

Both depth and duration of sedation were affected in a dose dependent manner in the 40 to 120 mcg/kg dosage range, as evidenced by the clinical assessment of depth of sedation, behavioral attitude, and other sedation-related responses. The sedation-related behavioral effects observed in this study included stance/posture, head ptosis, ear ptosis, eyelid drooping, and lip drooping. Similar effects are known to occur with other drugs in this class, the alpha$_2$-adrenoceptor agonists, when used in the equine.

Additionally, the physiological responses observed in this study were consistent with other drugs in this class. These transient effects included sweating, increased salivation, snoring (upper respiratory sounds), penile relaxation, lowered respiratory rate, decreased heart rate, 2° atrioventricular block, and a decrease in body temperature. Other responses (such as facial edema, pulse character, mucous membrane color, nasal discharge) were likely secondary to the behavioral and physiological effects previously noted.

The degree and duration of analgesia were shown to be affected in a dose related manner in the 40-120 mcg/kg dosage range by the response of the horses to thermal pain stimuli. These effects were demonstrated both objectively and subjectively.

One case of ventricular tachycardia and two minor unexpected adverse reactions (see below) were noted. One horse was diagnosed with pneumonia three days after receiving a 120 mcg/kg dose of romifidine.

The study demonstrates that the intravenous administration of romifidine HCl to horses, at dosages of 40-120 mcg/kg, is safe and effective.

(7) Adverse Reactions:

Reported adverse reactions, which were related to romifidine administration, included a single episode of ventricular tachycardia in an older horse with a previously existing IV/VI systolic cardiac murmur, one episode of shivering following each dose (in the same horse), and moderate ataxia in one horse during the first five minutes following the higher dose of romifidine. Ataxia is an expected effect for this class of drugs.

Preanesthesia Dose Confirmation Study:

Title: Dose Confirmation of SEDIVET 1% Injection (Romifidine HCl) for Use as a Premedicant to Ketamine or Thiopental Induction and Isoflurane Maintenance Anesthesia in the Horse (635-0290-97E-006)

(1) Type of Study: Clinical Study

(2) Investigator: William W. Muir,
Columbus, OH

(3) General Design:

(a) *Purpose:* This study was conducted to evaluate the use of SEDIVET as a preanesthetic prior to the induction of general anesthesia.

(b) *Animals:*

Number:	ten horses used in a crossover design
Sex:	mares and geldings
Breed:	Thoroughbred, Standardbred
Age:	4-14 years
Initial weight:	928-1309 lb (422-595 kg)

(c) *Control:* Not applicable

(d) *Test Article:* Injectable solution containing 1% romifidine HCl; final market formulation

(e) *Route of Administration:* Intravenous injection

(f) *Dose:* All horses received 100 mcg/kg b.w. romifidine HCl. Two treatments were administered to all ten horses, with a washout period of two weeks between treatments. One treatment used ketamine (2.2 mg/kg) for induction, and the other group was induced with thiopental (5.0 mg/kg). Following induction, all animals were maintained on isoflurane inhalant anesthesia for 30 minutes, then allowed to recover.

(g) *Test duration:* 18 days

(h) *Variables:*

Clinical evaluation:

1. Ambient temperature 2. Degree of ataxia 3. Behavioral attitude 4. Eyelid drooping 5. Lower lip drooping / lip separation 6. Clinical assessment of depth of sedation 7. Facial edema 8. Salivation 9. Cardiovascular	10. Respiratory 11. Penis relaxation (geldings) 12. Sweating 13. Skin temperature (touch) 14. Rectal temperature (probe) 15. Clinical assessment of depth of sedation 16. Response to touch 17. Observations/comments

Anesthesia evaluation: objective variables

1. Cardiac rate and rhythm 2. Respiratory rate 3. Mean arterial blood pressure (map) 4. Blood pH 5. Partial pressures of oxygen (paO_2)and carbon dioxide ($paCO_2$) 6. End tidal isoflurane concentration 7. Time from inducing agent injection to lateral recumbency	8. Time from recumbency to complete relaxation 9. Amount of additional anesthetic drugs required 10. Amount of dobutamine hydrochloride required 11. Time to sternal recumbency 12. Number of standing attempts 13. Time to standing

Anesthesia evaluation: subjective variables (excellent, good, fair, poor)

1. Quality of induction of anesthesia 2. Quality of transition to inhalational anesthesia 3. Quality of recovery from anesthesia

(4) Statistical Analysis:

Since the pre-anesthesia treatment, SEDIVET, was not compared to any other pre-anesthesia treatment only descriptive statistics are reported. Because this study included the pre-anesthetic combined with one of two anesthetic agents at the commencement of the study and the remaining anesthetic agent following a two week washout period, variables were summarized for each of the two anesthetic agents.

(5) Results:

The overall results of the physiological responses are listed in the following table.

Means (and ranges in parentheses) of Physiological Measurements of the Two Induction Groups

Variable	Time after Treatment Induction	Treatment			
		Ketamine		Thiopental	
Cardiac Rate (beats per minute)	10 minutes	31.4	(22-38)	30.8	(20-36)
	20 minutes	33.6	(26-40)	35.6	(28-44)
	30 minutes	37.2	(28-44)	38.2	(30-44)
Mean Arterial Blood Pressure (mm Hg)	10 minutes	117.4	(98-149)	106.9	(86-131)
	20 minutes	96.4	(69-141)	94.7	(62-116)
	30 minutes	84.7	(73-111)	81.8	(66-97)
End Tidal Isoflurane Concentration (%)	10 minutes	2.0	(1.2-2.4)	2.1	(1.8-2.5)
	20 minutes	2.0	(1.7-2.3)	2.1	(1.7-2.6)
	30 minutes	1.7	(1.5-2.0)	1.8	(1.5-2.1)

The overall results of the anesthetic responses are listed in the following table.

Means (and ranges in parentheses) of Anesthesia Variables of the Thiopental and Ketamine Induction Groups

Variable	Treatment*	
	Ketamine	Thiopental
Time from Induction to Lateral Recumbency (minutes)	2.5 (1-4)	1.4 (1-2)
Time from Lateral Recumbency to Anesthesia (minutes)	1.9 (1-3)	1.7 (1-3)
Amount of Anesthetic Drugs Required (mL)	11.7 (9.5-13.1)	51.1 (42.2-61.0)
Amount of Dobutamine Required (mL)	none	none
Time to Sternal Recumbency during Recovery (minutes)	32.7 (12-75)	53.7 (29-83)
Time to Standing Recovery (minutes)	38.7 (17-75)	61.0 (38-84)
Number of Standing Attempts	1.2 (1-3)	1 (1)

*both groups treated with 100 mcg/kg romifidine IV prior to induction

Thus, the dose of 100 mcg/kg SEDIVET produced moderate sedation without adverse

effects in all horses using either ketamine or thiopental. Pharmacological effects included:

reluctance to move
decreased response to touch and environmental stimuli
mild to moderate ataxia
decreased heart and respiratory rates
mild increase in body temperature (1.5°F)
second degree atrioventricular block

The quality of induction and transition to inhalant anesthesia were excellent following the administration of either induction agent, and the quality of anesthesia was considered to be excellent for all horses. The quality of recovery was excellent in all horses except one, scored as good, because the latter made three attempts before attaining a standing position. All other horses stood on their first attempt.

The post anesthetic period was typical of horses recovering from short term anesthesia. Compared to horses that received ketamine for induction, horses receiving thiopental for induction showed greater ataxia and longer sedation (40-60 minutes) during recovery from anesthesia.

(6) Conclusion: SEDIVET provides safe and effective sedation for induction to isoflurane anesthesia with either ketamine or thiopental. The behavioral and physiologic effects produced by SEDIVET were similar to other alpha$_2$-adrenoceptor agonists in horses. The cardiorespiratory effects recorded during isoflurane anesthesia, and the cardiorespiratory and behavioral effects recorded after anesthesia, were more indicative of the pharmacologic activity of the particular induction drug used rather than those of SEDIVET.

(7) Adverse Reactions: No adverse reactions were observed during the study.

3. *TARGET ANIMAL SAFETY:*

Acute Toxicity Study:

Title: An Investigation of the Safety of Exaggerated Doses of Romifidine in the Horse.

(1) Type of Study: acute toxicity study

(2) Investigators: Dr. W. McDonell, DVM, PhD, DVA, Diplomate ACVA
Guelph, Ontario, Canada
Dr. S. Young, Vet.MB, PhD, MRCVS, DVA
Guelph, Ontario, Canada

Dr. C. Kerr, DVM
Guelph, Ontario, Canada

(3) General Design:

(a) *Purpose*: This acute toxicity study was conducted to observe the effects of romifidine at dosages of 3X and 5X the highest labeled dose

(b) *Test Animals*: six adult horses (three per group)

(c) *Control Drug*: N/A

(d) *Dosage Form*: Injectable solution containing 10 mg/mL romifidine HCl (final market formulation)

(e) *Route of Administration*: a single, slow, intravenous injection (jugular)

(f) *Doses Used*: 360 mcg/kg (3X) and 600 mcg/kg (5X)

(g) *Test Duration*: two days

(h) *Variables Measured*:

Blood was sampled at baseline, 24 and 48 hours for venous blood gas analysis, hematology, and clinical chemistry. Clinically, the horses were evaluated for the degree of sedation, ataxia, heart rate and rhythm (ECG), and respiratory rate at 5, 10, 30, 60 minutes after drug administration, and hourly thereafter as long as drug effects were noted. The presence or absence of expected drug effects (cardiac arrhythmias, sweating, urination, respiratory stridor) and any unexpected side effects were recorded during four hours of continuous observation. No necropsies were performed.

(4) Results:

Intravenous overdoses of romifidine were administered to a total of six adult healthy horses divided into the following two groups:

Group 1 = 360 mcg/kg (3X the high end of the proposed dose range)
Group 2 = 600 mcg/kg (5X the high end of the proposed dose range)

No clinically significant changes were seen in blood gas, hematological, or serum biochemical values when 24 and 48 hour samples were compared to baseline.

Baseline mean heart rates declined from 35 bpm to 20 bpm approximately five minutes after romifidine administration, followed by a gradual increase over the next

eight hours of observation. Heart rate was only slightly lower in the 600 mcg/kg dose group compared to the 360 mcg/kg group; however, bradycardia and second degree atrioventricular heart block (seen on ECG) persisted longer in the higher dose group of horses.

No serious respiratory problems were noted. Occasional periods of apnea (twenty to forty seconds) were followed by several deep successive breaths. Mild respiratory stridor and snorting were noted.

All six horses experienced a similar degree of sedation, but the side effects (for example, ileus) persisted longer in horses in the higher dose group. Horses could be aroused by external stimuli, but then returned to an apparent deeply sedated state. No horses were severely ataxic. Sweating was observed. Gastrointestinal sounds were decreased for up to twelve hours (longer with higher dose). Frequent urination began at sixty to ninety minutes after romifidine administration and continued through the continuous four hour observation period.

(5) Statistical Analyses: None performed.

(6) Conclusion:

The study identified the expected side effects associated with romifidine as an alpha-2-agonist (bradycardia, heart block, respiratory stridor, ileus, colic, sweating, frequent urination). No abnormalities were seen in bloodwork. No horses died or became seriously ill from a single 3X or 5X dose of romifidine.

(7) Adverse Reactions:

During the study, gastrointestinal motility took six to twelve hours to return (as determined by auscultation). One horse showed mild abdominal discomfort twelve hours after administration of 600 mcg/kg romifidine. This horse was fed hay three hours after romifidine treatment, colicked twelve hours after treatment, was treated with flunixin meglumine and mild exercise, and recovered.

Only mild sweating was observed. Urination commenced at 60-90 minutes and occurred frequently through 4 hours.

Multiple Dosage Target Animal Safety Study:

(1) Type of Study: Target animal safety

(2) Investigators: Dr. G. Kehnscherper
O. Dietz, D.Sc.
Humboldt University
Berlin, Germany

(3) General Design:

(a) *Purpose*: This study was conducted to observe the toxicological responses of horses when romifidine is administered intravenously at dosages of 1X, 3X, and 5X the highest labeled dosage for up to 3 consecutive days.

(b) *Test Animals*: Nine horses divided into three groups (6 mares and 3 geldings), ages 3-15 years

(c) *Control Drug*: injectable saline

(d) *Dosage Form*: Injectable solution containing 10 mg/mL romifidine HCl (final market formulation)

(e) *Route of Administration*: a single, slow, intravenous injection (jugular)

(f) *Dosage Used*: 120 mcg/kg (1X), 360 mcg /kg (3X), 600 mcg/kg (5X)

Nine horses were divided into three groups (three horses per treatment group) and treated over 4 weeks with either romifidine or saline as follows:

	Week 1	Week 2	Week 3	Week 4
Group 1	-	120 mcg/kg romifidine for 3 days	-	saline for 3 days
Group 2	-	saline for 3 days	360 mcg/kg romifidine for 3 days	-
Group 3	120 mcg/kg romifidine once	-	saline for 3 days	600 mcg/kg romifidine for 3 days

The dosages represent 1X, 3X, and 5X the high end of the proposed dosage range. Dosages were administered at the same time of day for all treatments.

Blood samples were drawn at -10 min, 1, 24, 25, 48, 49, 72, 96 and 120 hours from horses that received any drug dosage for three consecutive days. Horses in group 3 that received 120 mcg/kg on only one day during week one were bled at -10 min, 1, 24, 48, and 72 hours.

(g) *Test Duration*: 2-4 weeks, depending on the group

(h) *Variables Measured*: ECG, arterial blood pressure, blood gases, heart rate, respiratory rate, body temperature, hematology and serum chemistry

(4) Statistical Analyses:

Repeated measures ANCOVA with a significant level of 0.10 was used to evaluate dose responses to romifidine treatment.

(5) Results:

Heart rate and rhythm: Romifidine produced heart rate and electrocardiographic effects typical of alpha$_2$-agonists: sinus bradycardia and first and second degree atrioventricular block. These effects were most pronounced within 30 seconds to 5 minutes following drug administration, and gradually subsided over the next 2 to 4 hours.

Other clinical findings: Pharmacological effects were transient. Difficulty in standing was observed in the 3X and 5X dosage groups. Sweating was noted in all romifidine groups. In the 1X group, blood pressure rose initially, followed by a return to baseline by 20-30 minutes. Fluctuations in blood pressure were noted during the first few minutes in the 3X and 5X groups, followed by an increase at five minutes, then a return to baseline beginning at one hour. Respiratory rates in all groups fell initially followed by a gradual increase toward baseline values. Body temperature response was varied, increasing slightly initially in the 1X and 3X groups, and decreasing slightly in the 5X group.

ECG results:

Dose	**Week 1 ECG results**
120 mcg/kg romifidine once (3 horses)	Two horses exhibited bradycardia, as well as first and second degree heart block between zero and thirty seconds after receiving romifidine. One of these two horses showed second degree heart block through the five minute time period, and at the four and eight hour ECG measurements. The third horse remained in atrial fibrillation after romifidine administration (this horse showed atrial fibrillation at every ECG measurement).

Dose	Week 2 ECG results
120 mcg/kg romifidine for three consecutive days	These three horses received saline during week 4. Romifidine at the high end of the 1X dose range caused sinus bradycardia (HR < 30 bpm), as well as first and second degree heart block in all three horses for varying time periods up to four hours. The horse with heart block up to four hours was the same horse that showed heart block after saline during week 4. Effects were most pronounced within thirty seconds to two minutes following romifidine administration.
Saline for three consecutive days	ECGs were normal.

Dose	Week 3 ECG results
360 mcg/kg romifidine for three consecutive days	Romifidine at the high end of the 1X dose range caused sinus bradycardia (HR < 30 bpm), and second degree heart block in all three horses for varying time periods up to 140 minutes. Effects were most pronounced within thirty seconds to two minutes following romifidine administration. One horse showed a single premature atrial depolarization at thirty and 100 minutes; the arrhythmias were not considered to be clinically significant or drug-related.
Saline for three consecutive days	Two horses showed normal ECGs; the other horse exhibited atrial fibrillation prior to and after saline administration on all three treatment days.

Dose	Week 4 ECG results
360 mcg/kg romifidine for three consecutive days	One horse demonstrated second degree heart block prior to and after romifidine administration that persisted through the four hour time period. Sinus bradycardia (HR<30 bpm) was also noted after romifidine. Another horse developed sinus bradycardia, first and second degree heart block that lasted between two and five minutes on all three days. The third horse persisted in atrial fibrillation prior to and after romifidine administration on all three days (the same horse that received saline during week 3 (before receiving romifidine), and experienced atrial fibrillation.

Saline for three consecutive days	All three horses exhibited normal ECGs, although one horse exhibited second degree atrioventricular heart block at most ECG recording time periods.

Blood pressure:

Group 1 = 120 mcg/kg for 3X duration:

Horses showed an initial transient rise in BP, followed by a rapid reduction within physiological levels lasting from 30 seconds to 10 minutes. Baseline values were reached approximately 20 to 30 minutes after romifidine administration.

Group 2 = 360 mcg/kg for 3X duration:

BP fluctuated for 2 minutes, followed by a dramatic and prolonged rise (BPsys=200 mmHg; BPdias=110 mmHg). BP remained elevated for approximately 60 minutes, and neared baseline values after 3 hours.

Group 3 = 120 mcg/kg for 1X duration:

BP increased 30 seconds after injection, falling again within 20 minutes and returning to baseline after 40 minutes.

Group 3 = 600 mcg/kg (5X) for 3X duration:

Results were similar to group 2: initial fluctuations followed by a dramatic rise for 2 to 60 minutes, and a gradual return to baseline by 3 hours. Elevated values were similar between the two groups (BPsystolic=210 mm Hg; BPdiastolic=110 mm Hg).

Body temperature:

Group 1 = 120 mcg/kg for 3X duration:

Mild decreases in rectal temperatures were noted; all returned to baseline within 8 hours.

Group 2 = 360 mcg/kg for 3X duration:

A slight rise over 30 to 60 minutes was followed by a slight reduction after 4 to 8 hours.

Group 3 = 120 mcg/kg for 1X duration:

Temperatures decreased over 1 to 2 hours and returned to baseline after 4 hours.

Group 3 = 600 mcg/kg (5X) for 3X duration:

Temperatures decreased continuously after one hour through the 8 hour timepoint; on day 3, measurements at 24 hours showed a return to baseline.

Blood gases:

Group 1 = 120 mcg/kg for 3X duration:

A slight reduction in pO_2 with a concomitant increase in CO_2 was seen in the group 1 horses. pH changes were unremarkable.

Group 2 = 360 mcg/kg for 3X duration:

Similar slight reductions in pO_2 and increases in CO_2 were seen in two horses in group 2. One horse showed no changes in blood gas parameters compared to placebo values.

Group 3 = 120 mcg/kg for 1X duration:

No significant changes were noted in blood gas parameters.

Group 3 = 600 mcg/kg (5X) for 3X duration:

Blood gas parameters within normal limits for all three horses.

Clinical pathology: There were small but statistically significant ($p<0.10$) differences in some blood parameters. Using a repeated measures, ANCOVA, statistically significant ($p<0.10$) dose responses to romifidine treatment were observed with increases in AST and total protein and decreases in creatinine and bilirubin. None of the changes were beyond the normal range and were not considered clinically significant.

Glucose values increased within the hour following each dose at 1, 24 and 48 hours. In most cases normal blood glucose returned by 24 hours.

At the 1X dosage, a slight decrease in hematocrit was seen, probably due to a decrease in erythrocyte count (but still within the normal reference range). A similar decrease was seen in some horses that received saline injections. At the 3X and 5X dosages,

the hematocrit increased one hour after romifidine administration in most horses in a non-dose dependent manner, but remained within the physiological range.

(6) Conclusions: Duration of sedation and analgesia were dose related. Effects of romifidine on heart rate and rhythm were typical of those produced by alpha$_2$-agonists (ataxia, bradycardia, hypertension followed by hypotension, second degree atrioventricular block, lowering of head, sweating, urination). Romifidine produced marked changes in cardiovascular function in healthy horses; these changes may become significant if administered to horses with compromised cardiovascular function.

The effects of romifidine on blood gases were minimal and not clinically significant in healthy adult horses. Body temperature increased slightly at the lower romifidine doses, and decreased during sedation with romifidine at the higher doses, returning to baseline in a dose dependent manner. Clinical pathology changes were not considered clinically significant. The transient increase in blood glucose is a recognized effect of alpha-$_2$ agonists. The increase is associated with insulin suppression and has an unknown clinical significance.

The study demonstrated that the intravenous administration of romifidine HCl to horses, at recommended doses is safe. Adverse reactions were seen at all dose levels. Some effects were dose-related, and all were typical of those seen with other alpha-$_2$ agonists.

(7) Adverse Reactions:

Incoordination and ataxia were frequently noted and were most obvious five to thirty minutes after romifidine administration. One 3X dose horse fell but was able to rise immediately.

Hypertension, hypotension, and bradycardia occurred following administration of romifidine at all doses. It could not be determined from the data whether the frequency and duration of cardiac arrhythmias increased with increases in dose.

Occasional signs of paradoxical excitation were noted in some horses. Other side effects included increased urination 80 minutes after romifidine administration, sweating, salivation, flatulence, and edema of the head and lower abdomen (due to lowering of the head).

4. HUMAN SAFETY:

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows:

"Not for human use. Keep this and all drugs out of the reach of children.

Not for horses intended for human consumption.

Although apparently deeply sedated, some horses may still respond to external stimuli with defensive movements (e.g., kicking). Sedated horses are frequently ataxic. Routine safety measures should be used to protect practitioners and handlers.

Romifidine hydrochloride can be absorbed and may cause irritation following direct exposure to skin, eyes or mouth. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. In case of accidental oral exposure or injection, seek medical attention. If irritation or other adverse reaction occurs (for example, sedation, hypotension, bradycardia), seek medical attention.

As with all injectable drugs causing profound physiological effects, precautions should be taken by practitioners to prevent accidental self-injection when handling and using filled syringes. Users receiving treatment for blood pressure abnormalities should take special precaution to avoid exposure to this product.

Note to Physician: This product contains an α_2-adrenoreceptor agonist and can be absorbed by oral and dermal routes."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that SEDIVET, when used under the labeled conditions of use, is safe and effective for use as a sedative and analgesic to facilitate handling, clinical examinations, clinical procedures, and minor surgical procedures in adult horses. SEDIVET is also indicated as a preanesthetic prior to the induction of general anesthesia in adult horses.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the level of sedation and analgesia required for the various procedures during which this drug may be used. Professional veterinary expertise is also necessary to administer anesthetics associated with the use of this drug as a preanesthetic, and to monitor patients for the adverse effects of this drug.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

SEDIVET is under the following U.S. patent number:

U.S. Patent Number	Date of Expiration
4,624,960	October 11, 2005

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

Package insert
Vial label
Box label for individual vial
Shipping label

314301L-00-0403

NADA 141-229, Approved by FDA

Sedivet® 1.0% Injection

(romifidine hydrochloride)

Boehringer Ingelheim

Sedative and analgesic drug for intravenous use in horses only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: Sedivet 1.0% Injection (romifidine hydrochloride) is an α_2-adrenoceptor agonist with sedative and analgesic properties. The chemical name is 2-bromo-6-fluoro-2-imidazolidinyliden-benzamine-monohydrochloride. It is a crystalline, white, odorless, water soluble substance with a molecular formula of $C_9H_9BrFN_3$•HCl, and a molecular weight of 294.56. Each mL contains 10 mg romifidine hydrochloride, 6.5 mg sodium chloride, 2 mg chlorocresol, and water for injection.

Indications: Sedivet 1.0% Injection is indicated for use as a sedative and analgesic to facilitate handling, clinical examinations, clinical procedures, and minor surgical procedures in adult horses. Sedivet 1.0% Injection is also indicated as a preanesthetic prior to the induction of general anesthesia in adult horses.

Dosage and Administration: *Sedation and Analgesia Dose:* Administer slowly as a single IV injection using a dosage range of 40 - 120 µg/kg (0.4 - 1.2 mL/100 kg body weight) depending on the depth and duration of sedation that is required. The onset of action occurs in 30 seconds to 5 minutes, and gradually subsides during the next 2 to 4 hours. Degree of sedation and analgesia is dose-and time-dependent; therefore, more profound analgesia will occur with larger doses, as well as closer to the time of injection.

Note: The animal should be allowed to rest quietly for several minutes prior to and following injection.

Note: The duration of analgesia is shorter than the duration of sedation.

Sedation Dose	Onset of Sedation*	Duration of Sedation	Onset of Analgesia	Duration of Analgesia
40 µg/kg (0.4 mL/100 kg)	2-4 minutes	75 minutes	5 minutes	30 minutes
120 µg/kg (1.2 mL/100 kg)	2-4 minutes	3 hours	5 minutes	150 minutes

*Times reported are from the sedation dose confirmation study (see Effectiveness).

Preanesthesia Dose: A single IV injection using a dose of 100 µg/kg (1.0 mL/100 kg body weight) was shown to be effective in the preanesthesia dose confirmation study (see Effectiveness). Anesthesia should be induced after maximum sedation is achieved. The administration of α_2-agonists results in anesthetic sparing effects[1,2]; therefore, anesthetic doses should be reduced to avoid overdose.

Mild to moderate sedation occurs within 2-4 minutes. Following induction, lateral recumbency occurs within 4 minutes, followed by complete anesthesia within 6-16 minutes. During recovery from anesthesia, sternal recumbency occurs within 12-83 minutes, followed by standing in 17-84 minutes. Recovery time is primarily determined by the choice of induction anesthetic and/or the duration of anesthesia.

Contraindications: Sedivet 1.0% Injection is contraindicated in horses with known hypersensitivity to romifidine.

Intravenous potentiated sulfonamides should not be used in anesthetized or sedated horses as potentially fatal cardiac dysrhythmias may occur.[3]

Warnings: Not for human use. Keep this and all drugs out of the reach of children.

Not for horses intended for human consumption.

Although apparently deeply sedated, some horses may still respond to external stimuli with defensive movements (for example, kicking). Sedated horses are frequently ataxic. Routine safety measures should be used to protect practitioners and handlers.

Romifidine hydrochloride can be absorbed and may cause irritation following direct exposure to skin, eyes or mouth. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. In case of accidental oral exposure or injection, seek medical attention. If irritation or other adverse reaction occurs (for example, sedation, hypotension, bradycardia), seek medical attention.

As with all injectable drugs causing profound physiological effects, precautions should be taken by practitioners to prevent accidental self-injection when handling and using filled syringes. Users receiving treatment for blood pressure abnormalities should take special precaution to avoid exposure to this product.

Note to Physician: This product contains an α_2-adrenoceptor agonist and can be absorbed by oral and dermal routes.

Precautions: The use of Sedivet 1.0% Injection with other α_2-agonists is not recommended since the effects (for example, cardiovascular changes, respiratory depression, ataxia) could be additive.

The adverse effects of Sedivet 1.0% Injection may be potentiated by the administration of other sedatives, tranquilizers, or opioids.

The use of epinephrine should be avoided since epinephrine may potentiate the effects of α_2-agonists.

Anesthetic doses should be reduced in the presence of Sedivet 1.0% Injection to avoid excessive depression of the central nervous system.

Sedivet 1.0% Injection has not been evaluated in horses with compromised cardiovascular function. The effects of bradycardia, increased vascular resistance, decreased cardiac output, and respiratory depression could be significant in horses with primary myocardial disease, or circulatory shock.

Sedivet 1.0% Injection should not be used in horses with respiratory disease, hepatic or renal disease, dehydration, or other systemic conditions of compromised health.

The effects of Sedivet 1.0% Injection have not been evaluated in horses with colic.

The effects of Sedivet 1.0% Injection have not been evaluated in pregnant mares, in horses intended for breeding, or in foals.

Adverse Reactions: As with other drugs of this class, the administration of Sedivet 1.0% Injection causes bradycardia (possibly profound), first and second degree atrioventricular heart block, and hypotension. The frequency and duration of cardiac arrhythmias have been shown to be dose related.

The following commonly occurring adverse reactions have been noted using α_2-agonists: hypertension, hypotension, bradycardia, ataxia, piloerection,

sweating, muscle tremors, salivation, penile relaxation, urination (about an hour after treatment), lowering of head (causing passive congestion and swelling of face, lips, upper airways), stridor, decreased gastrointestinal motility, flatulence, and mild colic.

The potential exists, as with all α_2- agonists, for isolated incidences of excitation (paradoxical response).

Rare anaphylactic reactions have been reported, including one or more of the following: urticaria, dyspnea, edema of the upper airways and head, trembling, recumbency, and subsequent death.

To report adverse reactions and/or to obtain a copy of the Material Safety Data Sheet (MSDS), call 1-800-821-7467.

Clinical Pharmacology: Romifidine is a potent α_2-adrenoceptor agonist that produces sedation and analgesia. Sedation is induced by stimulation of presynaptic α_2- receptors in the central nervous system. Administration of romifidine to conscious or anesthetized horses results in a biphasic effect on blood pressure. A transient increase in blood pressure due to peripheral vasoconstriction is followed by a compensatory vagal baroreceptor response resulting in longer lasting hypotension and bradycardia. A transient change in the conductivity of the cardiac muscle may manifest clinically as a partial atrioventricular block. Peripheral vasoconstriction may also lead to a transient reduction in gastrointestinal motility.

Effectiveness: A field study was conducted to evaluate romifidine as a sedative or a preanesthetic. Clinicians selected an appropriate dose, based on the procedure. Sedative doses ranged between 30-100 µg/kg; preanesthetic doses ranged between 40-100 µg/kg. The quality of sedation was rated as "good" or "excellent" in 18 of 23 horses. Of the remaining five horses evaluated for sedation, three were rated as "fair" and two were rated as "poor". When used for preanesthesia, inductions were rated as "well-controlled" in 16 of 23 horses. Recoveries from anesthesia were evaluated as "satisfactory" or "excellent" in 20 of 23 horses. Two horses required more than three attempts to stand. One horse was euthanized without recovery, due to an unfavorable diagnosis unrelated to drug administration.

In a sedation dose confirmation study with a crossover design, twenty horses were used to evaluate romifidine at two doses: 40 and 120 µg/kg. Clinical assessments of depth of sedation, behavioral attitude, stance/posture, head ptosis, ear ptosis, eyelid and lip drooping were evaluated. Depth and duration of sedation were affected in a dose dependent manner. By the response of the horses to thermal noxious stimuli applied to withers and fetlock, the degree and duration of analgesia were also shown to be dose dependent. Transient physiological and clinical effects included decreased respiratory and heart rates, second degree atrioventricular block, sweating, increased salivation, stridor, penile relaxation, and a slight decrease in body temperature. Seventy-five minutes after receiving the 40 µg/kg dose, one older horse with a preexistent grade IV/VI systolic murmur, experienced ventricular tachycardia that lasted for 11.5 minutes. Another horse was diagnosed with pneumonia three days after receiving the 120 µg/kg dose of romifidine.

In a separate preanesthesia crossover study, the effectiveness of the 100 µg/kg preanesthetic romifidine dose was confirmed. Ten horses were induced with either ketamine or thiopental, followed by isoflurane maintenance anesthesia. The quality of induction, the transition to inhalant anesthesia, and the quality of anesthesia were scored as "excellent" for all horses. All horses except one stood on the first attempt (one stood on the third attempt).

Animal Safety: A toxicity study was conducted to observe the effects of a single dose of Sedivet 1.0% Injection at 360 µg/kg (3X the highest recommended dose) and 600 µg/kg (5X dose), using 3 horses per group. There were no clinically important alterations of blood gas, acid-base, hematological, or clinical chemistry values. The duration of bradycardia and second degree heart block was longer using the higher dose. Occasional periods of apnea (20 to 40 seconds) were followed by several deep successive breaths. Mild respiratory stridor was present, and horses periodically exhaled forcefully ("snorting") in an apparent effort to clear their upper airways. The duration of sedation was dose dependent.

Horses exhibited signs of deep sedation, but would occasionally respond to environmental stimuli, only to return to deep sedation shortly thereafter. Mild sweating was observed. Urination commenced at 60-90 minutes and occurred frequently through four hours. One horse, which had been given a small amount of hay before full gastrointestinal motility had returned, showed mild abdominal discomfort twelve hours after administration of 600 µg/kg romifidine. Horses in this study were not necropsied. Toxicity study results for another product in the α_2-agonist class, showed microscopic foci of myocardial necrosis during histopathological examination in one of eight horses that received ten times the high end of the recommended dose for that product.

In another safety study, Sedivet 1.0% Injection was administered IV at doses of 120 µg/kg (1X the highest recommended dose), 360 µg/kg (3X), and 600 µg/kg (5X) for up to 3 consecutive days (9 horses per group). Sinus bradycardia (<30 bpm) and second degree heart block were most pronounced within 30 seconds to 5 minutes, gradually subsiding over two to four hours. Severe ataxia was observed in the 3X and 5X dose groups. Sweating was noted in all romifidine groups. Horses receiving the 1X dose showed an initial rise in blood pressure, followed by a return to baseline by 20-30 minutes. In the 3X and 5X groups, increases in blood pressure were seen at five minutes; returning toward baseline after 1 hour. Respiratory rates in all groups fell initially, followed by a gradual increase toward baseline values. Body temperature response varied, increasing slightly in the 1X and 3X groups, and decreasing slightly in the 5X group.

Storage Information: Store at controlled room temperature, 59-86°F (15-30°C).

How Supplied: Sedivet 1.0% Injection is supplied in 20 mL multi-dose vials containing 10 mg romifidine hydrochloride per mL.

References:

1 Muir, WM. Anesthesia for the equine patient. World Equine Vet Rev 1998; 3(4):27-29.

2 England, GCW, Clarke, KW. Alpha$_2$ adrenoceptor agonists in the horse – a review. Br Vet J 1996; 152:641-657.

3 Taylor PM, et al. Possible potentiated sulphonamide and detomidine interactions. Vet Rec 1988; 122:143.

Sedivet® is a registered trademark of Boehringer Ingelheim Vetmedica GmbH, licensed to Boehringer Ingelheim Vetmedica, Inc.

Manufactured by:
Boehringer Ingelheim Vetmedica, Inc.
St. Joseph, MO 64506 U.S.A.

314301L-00-0403
Code 314311
Revised 03/2004

Sedative and analgesic drug for intravenous use in horses only

Warning: Not for human use. Keep this and all drugs out of the reach of children

Not for horses intended for human consumption

Store at controlled room temperature, 59–86°F (15–30°C)

NADA 141-229, Approved by FDA

314302L-00-0403
Code 314311
Revised 03/2004

Manufactured by:
Boehringer Ingelheim Vetmedica, Inc.
St. Joseph, MO 64506 U.S.A.

Sedivet®

(romifidine hydrochloride)
1.0% Injection

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian

Net Contents: 20 mL

Each mL contains: 10 mg romifidine hydrochloride, 6.5 mg sodium chloride, 2 mg chlorocresol, and water for injection

Indications: Sedivet (romifidine hydrochloride) 1.0% Injection is indicated for use as a sedative and analgesic to facilitate handling, clinical examinations, clinical procedures, and minor surgical procedures in adult horses. Sedivet 1.0% Injection is also indicated as a preanesthetic prior to the induction of general anesthesia in adult horses.

Dosage and Administration: Refer to package insert for complete dosage and administration information.

Lot No.: Exp. Date:

Boehringer Ingelheim

314303D-00-0403

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Not for horses intended for human consumption.

Contraindications: Sedivet 1.0% Injection is contraindicated in horses with known hypersensitivity to romifidine.

Intravenous potentiated sulfonamides should not be used in anesthetized or sedated horses as potentially fatal cardiac dysrhythmias may occur.

Refer to package insert for additional information.

Store at controlled room temperature, 59–86°F (15–30°C).

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314303D-00-0403
Code 314311
Revised 03/2004

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Lot No.: Exp. Date:

314303D-00-0403

Sedivet 1.0% Injection
(romifidine hydrochloride)

QUANTITY LOT NO. EXP. DATE

24x20mL

ITEM NUMBER

314311000

10012313314313

Store at controlled room temperature 59-86°F (15-30°C).

Manufactured by:
Boehringer Ingelheim Vetmedica, Inc
St. Joseph, MO 64506

314304C-00-0403